SPECIAL COMMUNICATION

A research agenda for assessing the potential contribution of genomic medicine to tobacco control

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This paper identifies research priorities in evaluating the ways in which ''genomic medicine''—the use of genetic information to prevent and treat disease—may reduce tobacco-related harm by: (1) assisting more smokers to quit; (2) preventing non-smokers from beginning to smoke tobacco; and (3) reducing the harm caused by tobacco smoking. The method proposed to achieve the first aim is ''pharmacogenetics'', the use of genetic information to optimise the selection of smoking-cessation programmes by screening smokers for polymorphisms that predict responses to different methods of smoking cessation. This method competes with the development of more effective forms of smoking cessation that involve vaccinating smokers against the effects of nicotine and using new pharmaceuticals (such as cannabinoid antagonists and nicotine agonists). The second and third aims are more speculative. They include: screening the population for genetic susceptibility to nicotine dependence and intervening (eg, by vaccinating children and adolescents against the effects of nicotine) to prevent smoking uptake, and screening the population for genetic susceptibility to tobacco-related diseases. A framework is described for future research on these policy options. This includes: epidemiological modelling and economic evaluation to specify the conditions under which these strategies are cost-effective; and social psychological research into the effect of providing genetic information on smokers' preparedness to quit, and the general views of the public on tobacco smoking.

''Genomic medicine'' is a phrase used to describe the use of genomic knowledge to improve human health by increasing our ability to prevent and treat human disease, which it is claimed will revolutionise healthcare.[1 2] ''Predictive genomic medicine'' involves screening healthy people to identify those who carry alleles that increase their susceptibility to diseases such as cancer and heart disease. People found to be at higher genetic risk of these disorders would be advised to change their behaviour (eg, stop smoking, exercise or eat a healthier diet) or be offered drugs or other medical treatment to reduce their chances of developing these diseases. ''Pharmacogenetics'' is a genomic strategy that aims to use genetic information to identify the type of treatment that will maximise an individual's chances of a good outcome.[2]

Given the major contribution that tobacco smoking continues to make to disease burden, and the claims made for genomic medicine, it is important for the tobacco control field to begin to explore the ways in which genomic medicine may or may not contribute to the reduction of tobacco smoking and tobacco-related disease. This paper outlines a research agenda to identify the most promising applications of genomic medicine to tobacco control. It begins with the most plausible and currently active field of research, the pharmacogenetics of treating nicotine dependence.[3] It assesses this option against the main competitive strategy, searching for more effective smoking cessation treatments, and outlines the type of research required to evaluate its role.

The paper then considers the more speculative predictive use of genetic information in screening for susceptibility alleles for nicotine dependence and tobacco-related disease. It says why this strategy is least likely to be useful. Despite the fact that this possibility remains speculative, entrepreneurs have begun to market genetic tests directly to consumers that they claim will provide people with information about their genetic susceptibility to addiction.[4] The tobacco-control field therefore needs to be ready to explain to policy makers and the general public why these options are unlikely to deliver the benefits claimed by their proponents.

THE GENETICS OF TOBACCO SMOKING

Twin studies of cigarette smoking in developed countries estimate that the heritability of smoking initiation is 50%,[5 6] whereas the heritability of nicotine dependence may be as high as 70%.[5 7] Plausible ''candidate genes'' are present that increase the risks of nicotine dependence. These are polymorphisms (variant alleles found in >1% of the population) that affect an individual's risk of developing nicotine dependence by affecting peripheral nicotine metabolism[8] and the brain's response to nicotine via levels of central dopamine receptors and transporters, (eg [3 9 10]) neurotransmitters implicated in mediating the rewarding effects of drugs, food and sex in the nucleus accumbens of the forebrain.[11 12]

The candidate genes that have been investigated to date have not been consistently found in all association studies.[5 13] This has led some geneticists to question the value of searching for addiction susceptibility genes,[14] but others[15] remain optimistic that the recent completion of the haplotype map will improve the efficiency of gene searches and the replicability of results.[16]

On the available data, the most plausible hypothesis is that the inheritance of smoking is polygenic—that is, there are multiple genes of small effect involved.[7 10 17 18] Meta-analyses of susceptibility alleles for 55 different medical conditions (including psychiatric and behavioural disorders) suggest that the susceptibility genes which are replicated only modestly increase the risk—that is, increase the risk of the disorder 1.2–1.5 times.[19 20] These modest associations have major implications for the plausibility of predictive genetics, as discussed below.

USING GENETICS AND NEW BIOTECHNOLOGIES TO IMPROVE SMOKING CESSATION

Assessing the pharmacogenetics of smoking cessation

Current pharmacological aids to smoking cessation either replace the nicotine delivered by cigarettes (nicotine replacement therapy (NRT))[21] or act on central nervous system sites to

Abbreviations: DRD2, dopamine D2 receptor; NRT, nicotine replacement therapy

reduce withdrawal symptoms (bupropion) during smoking cessation.[22] These approaches improve on smoking cessation rates produced by self-quitting and behavioural interventions[23 24]; they are also cost effective.[25] Nevertheless, only a minority of smokers succeed in quitting using these methods.[26]

Pharmacogenetics is suggested as a way of improving the modest success of smoking cessation. Genetic information (eg, about nicotine metabolism or dopamine response to nicotine) could be used to match smokers to the treatment most likely to enable them to quit using buproprion or NRT.[3 12 27] A pharmacogenetic test for nicotine dependence—NicoTest—has been marketed in the UK via direct to consumer advertising as a way of helping smokers to decide whether to use NRT or bupropion in a quit attempt.

The two major questions that arise while assessing nicotine pharmacogenetics are: (1) is this approach effective—that is, do the genotypes identified predict differential responses to treatment? If so, (2) will the additional costs of genetic testing be justified by the increases in cessation rate produced?[28]

If we assume that the answer to the first question is positive, how would we assess the cost-effectiveness of nicotine pharmacogenetics? We know that the cost-effectiveness of pharmacogenetic tests is affected by the characteristics of: the genes being tested, the condition being treated, and the treatments that genetic tests are being used to select among.[28]

Among the key characteristics of the gene being tested are its prevalence in the population of smokers and how well it predicts differential treatment response. Screening for rare polymorphisms is not very useful unless they are very strong predictors of treatment outcome, as a very large number of people will need to be tested to identify the small number of people who respond differentially to treatment. The predictive value of the polymorphisms for the outcome of interest (eg, differential response to smoking cessation interventions) reflects the sensitivity and specificity of the genetic test for the polymorphisms and the penetrance of the gene—that is, the degree to which people with the polymorphism differ in their response to treatment from those who do not. A genetic test for a gene of low prevalence and penetrance is unlikely to be useful.[28] This describes the alleles that have been evaluated in studies of nicotine pharmacogenetics to date.[3]

We can specify the type of research required to assess the cost-effectiveness of nicotine pharmacogenetics using NicoTest as an example. Nicotest uses the results of a genetic test for a polymorphism in the dopamine D2 receptor (DRD2) allele to determine whether a smoker is more likely to quit smoking using NRT or buproprion (http://www.nicotest.com/). One could model the cost-effectiveness of NicoTest using empirical evidence on: the prevalence of the DRD2 polymorphism among smokers; its predictive value for success in quitting with NRT or bupropion; the cost charged for the test; epidemiological models of the tobacco-related mortality and morbidity that would occur among smokers who continue to smoke versus those who successfully quit using these methods; and estimates of the costs of treating tobacco-related disease that have been averted by successful quitting.

The critical issue in evaluating the cost-effectiveness of NicoTest is the condition with which we compare its cost-effectiveness. A comparison condition is required to decide whether the improvement in cessation rate achieved by NicoTest is worth the additional costs incurred by the genetic testing and counselling that its use entails.[27 28] This will require studies that compare the cost-effectiveness of NicoTest with simpler and cheaper methods of treatment selection, such as avoiding matching by offering all patients the most effective treatment (averaged across genotypes).[7] The critical measure in this case will be the incremental cost-effectiveness ratio: the ratio of the difference in benefits between using NicoTest and not matching, divided by the difference in costs between these two approaches.[28]

In addition to cost effectiveness, evaluations of NicoTest will need to consider the social and psychological consequences of giving smokers information about their genetic susceptibility to nicotine dependence. The implicit assumption of pharmacogenetics is that this information will motivate smokers to use the treatment provided, but this cannot be simply assumed.[29] We need to investigate the ''folk genetics'' of nicotine dependence: the everyday inferences that people in the community draw about the plasticity of smoking and its amenability to intervention if it is seen as being in some sense ''genetic''. Specifically, we need to discover whether popular simplifications of smoking ''genetics'' entails a form of genetic reductionism[30]—namely, the belief that smoking is a fixed and immutable behaviour that can only be changed with great difficulty, if at all, by biological interventions.[29 31 32] Two studies carried out to date on smokers' understanding of the implications of information about genetic risk for cessation[33 34] suggest that smokers who accept the plausibility of a genetic contribution to cigarette smoking are less confident about their self-efficacy in quitting and more likely to see a biological intervention as required to become abstinent. More work is required on this issue.

Searching for more effective smoking cessation treatments

There would be less reason to investigate nicotine pharmacogenetics if we could substantially improve the efficacy of smoking cessation methods. The development of several new aids to smoking cessation treatment that have recently been approved or are currently being trialled promises to improve on the modest efficacy of NRT and bupropion.

One of these new methods that has captured a great deal of media and popular interest is the ''nicotine vaccine''. This is an immunotherapeutic approach to smoking cessation that induces the immune system to produce antibodies that bind to nicotine and prevent it from crossing the blood–brain barrier to act on receptors in the brain.[35–37] Animal studies have shown that attaching nicotine to a suitable antigenic protein[35 38 39] produces antibodies that have a high affinity for nicotine and prevent it from reaching the brain.[39] Vaccination of animals attenuates nicotine effects[40] and suppresses dopamine release in the nucleus accumbens.[38 41]

At least three biotechnology companies (Cytos (Zurich, Switzerland), Nabi (Florida, USA) and Xenova (Cambridge, UK)) are developing a type of nicotine vaccine.[42] Successful phase 1 trial results have been published on one of the vaccines[43] and phase 2 human clinical trials are in progress on all three vaccines.[42] Early reports of abstinence rates at 6 months released by some of these companies[44–46] look promising, but no detailed reports have yet been published in peer-reviewed journals.

Active vaccination against nicotine could be used to reduce relapse to smoking in abstinent smokers. Nicotine antibodies would attenuate the pharmacological effects of nicotine during the first few months after quitting when most smokers relapse, thereby reducing the chance that a slip will produce a return to daily smoking.[37] A nicotine vaccine would not be perfectly effective, as it could be circumvented by increasing the dose of nicotine. Nonetheless, attenuating the rewarding effects of nicotine may be enough to reduce relapse rates in smokers by making a lapse less likely to lead to a return to daily smoking.[47]

A nicotine vaccine has several potential advantages over NRT and bupropion. Firstly, it does not require daily dosing: an active vaccine administered two to four times could produce immunity that would last for several months.[48] Less frequent dosing should ensure better compliance.[37] Secondly, as the

nicotine antibodies do not act in the brain, they are likely to have fewer adverse side effects. Finally, a nicotine vaccine can also be used in combination with bupropion to reduce withdrawal and depressive symptoms in abstinent smokers.[37]

The cost-effectiveness of a nicotine vaccine can be evaluated using an approach similar to that used to model the cost-effectiveness of NicoTest—that is, by comparing its likely cost effectiveness with that of the best available current treatment, bupropion. In the absence of data on efficacy and vaccine costs, this approach to modelling would involve estimating how much more effective than bupropion a nicotine vaccine would need to be, for a given cost, to qualify as a cost-effective smoking cessation intervention.

Several uncertainties exist about a nicotine vaccine, the significance of which is more difficult to assess. One such uncertainty is the effect of public concerns about the safety of vaccines against childhood infectious diseases[49 50] on the perceived safety and, consequently, on the uptake of a nicotine vaccine. This issue will need to be explored by assessing the interest in and attitudes of current smokers towards using a nicotine vaccine to quit smoking. A second uncertainty arises from the potential preventive use of nicotine vaccines in children and adolescents. This possibility (which is discussed below) may overshadow the more promising use of a vaccine for smoking cessation in adults.

A third type of uncertainty concerns the challenges that a nicotine vaccine faces from new pharmaceuticals for smoking cessation. Specifically, it is uncertain whether competitive nicotine vaccines will prove to be cost-effective with a nicotine receptor partial agonist, varenicline,[51 52] and rimonabant, a cannabinoid antagonist that has been approved for the treatment of obesity and that also shows promise in treating nicotine dependence.[26 53] A smoking cessation drug that avoided weight gain would be enormously attractive to many smokers even if it was no more effective than current cessation pharmacotherapies.[26]

Methods have been developed for evaluating the cost-effectiveness of new pharmaceuticals[54] and evidence from such analyses is routinely required in making decisions on the public subsidy of new drugs in Australia.[55] The research challenge for the tobacco control community will be adapting these methods to provide comparable evaluations of the cost effectiveness of new pharmaceuticals, nicotine vaccines and nicotine pharmacogenetics to assist policy makers in deciding which policies are worthy of support.

USING NEW BIOTECHNOLOGIES TO PREVENT SMOKING AND SMOKING-RELATED DISEASES

Predictive testing for the genetic risks of nicotine dependence

If susceptibility genes for nicotine dependence are identified (possibly as a result of the increased efficiency of gene hunting made possible by the haplotype map project), then it would be possible in principle to screen the population for susceptibility to nicotine dependence and provide preventive behavioural and pharmacological interventions to people who are at higher genetic risk.[1] The obvious objection is that it is not good public health policy to encourage people to smoke tobacco, regardless of their genetic risk. Nonetheless, the idea has a popular appeal in the media[56] and genetic tests are now being marketed for this purpose in the USA; hence, it is important that the tobacco control field explains to the community and their political representatives why it is not good public health policy to screen the population for genetic susceptibility to nicotine dependence.[57]

1. Individual alleles that have been identified to date (eg, DRD2) only weakly predict an increased risk of various forms of drug dependence (with an average relative risk of 1.45).[58]
2. Risk prediction for people does not improve a great deal if we test multiple susceptibility alleles.[59] Testing multiple genetic variants that are individually weak predictors will improve prediction (eg, if the results of tests of multiple susceptibility alleles are combined via regression to produce a risk score[60 61]). However, in general, the greater the number of genes that are involved in disease susceptibility, the less useful most people will find the information about their genotype. This is because the risk distribution for multiple alleles (assuming that the risks are multiplicative) will be approximately log normal. Consequently, the number of people who have multiple genes that confer either a very high or a very low risk of nicotine dependence will be small and most people screened will prove to be at ''average'' genetic risk.[7 60]
3. Given the low prevalence of high-risk combinations of susceptibility gene variants, a large number of people would need to be screened to identify the few at highest risk.[62–64] This and the preceding point are illustrated in Yang *et al*'s[65] simulation of the performance characteristics of a test that screens for five susceptibility alleles, each with a relative risk (RR) of disease that ranged from 1.5 to 3.5 and a prevalence in the population between 0.10 and 0.25. These genes were also assumed to interact with a relatively common environmental exposure (with a prevalence of 15%) and an RR of 2. Computer simulations showed that the prediction of disease risk was substantially improved by testing for the five alleles. For example, people who screened positively on all five genes had an 81% chance of developing the disease and this increased to 89% if they had been exposed to the risk factor. However, the number of people who possessed this combination of genes and environmental exposure was very small: only 3.75 in 100 000 people would have all five susceptibility alleles and <1 (0.6) in 100 000 would have the five alleles and the environmental exposure. Hence, 250 000 people would need to be screened to identify 1 person who had $>80\%$ chance, and 1266 people would need to be screened to identify one person with $>50\%$ chance, of developing the disease.
4. Screening is ethically justifiable only if there is an effective intervention to prevent the disorder in those who are identified as being at increased risk.[59 64 66] No interventions are seen at present, apart from advice to ''avoid smoking'', which is good advice regardless of one's genetic susceptibility to nicotine dependence. The possibility of preventive vaccination is discussed below.
5. As was the case with nicotine pharmacogenetics, we also need to know what the psychological effects will be of giving people information about their genetic risk of nicotine dependence. Unintended adverse effects could occur—for example, if telling adolescents about their susceptibility to nicotine dependence increased their curiosity to try smoking or reduced their likelihood of later attempting to quit if they did smoke tobacco. These possibilities also need to be explored in studies of the psychological effect of providing genetic information.[29]
6. We would need to explore the effects of providing genetic information about nicotine dependence on health or life insurance, and the possible social stigmatisation of those who are identified as being at increased ''genetic risk''. The social stigmatisation could arise because of pleitropy—the fact that the genes that predict an increased risk of nicotine dependence may also predict an increased risk of other more stigmatised disorders. This is the case

with the DRD2 allele that is used in NicoTest and marketed as an addiction susceptibility genetic test. It is also associated (albeit modestly) with an increased risk of alcohol dependence, compulsive gambling, and addiction to heroin and cocaine.[58 67]

Screening for genetic susceptibility to tobacco-related diseases

Genetic factors appear to play a part in susceptibility to some types of cancer, including lung cancer,[68] although there is disagreement about how large a part they play.[69–72] Polymorphisms may also affect the likelihood of smokers developing heart disease[73] and chronic obstructive lung disease.[74] These findings raise a possibility that ambivalent smokers may find attractive—namely, that they could be screened for susceptibility genes that predicted an increased risk of smoking-related diseases if they smoked and that, if they were at low genetic risk, they could continue to smoke with impunity.[75]

On the basis of the available evidence, this option is even more impractical than screening for genetic susceptibility to nicotine dependence for reasons that need to be clearly communicated to the public. Firstly, since multiple genes are probably involved in susceptibility to tobacco-related diseases, the ability to predict disease risk may not improve on predicting risk from being a smoker. Secondly, cigarette smoking causes multiple diseases, the most common being lung and other cancers, heart disease and chronic obstructive lung disease. This means that predicting the genetic risk of developing even only the most common tobacco-related diseases would involve testing individuals for a large number of polymorphisms.

Thirdly, very few smokers would be at low risk of developing all smoking-related diseases. Indeed, most smokers would be at increased genetic risk for at least one smoking-related disease,[75] as can be illustrated by some simple calculations. Let us assume that there are only six susceptibility alleles (each with an RR of 1.5, a prevalence of 10% and with multiplicative risks) for each of the five major tobacco-related diseases (lung cancer, coronary heart disease, chronic lung disease, other cancers and stroke). As per these assumptions, only 3% of smokers would be at low risk of developing all five diseases; the remainder would have an increased risk of developing at least one of the diseases.

Preventive uses of a nicotine vaccine

The term nicotine vaccine suggests the possibility that children can be given lifelong immunity to smoking that may prompt parents to vaccinate their children.[76] As minors, children would not be legally able to consent to vaccination, but some say that as parents already make choices for their children that affect their lives (eg, their diet and education), vaccination against drugs is just another decision that parents should be able to make on behalf of their children.[76] These are thorny ethical issues.[77]

Even if we set the ethical issues aside, there are good practical reasons why we should not rush into using a nicotine vaccine to prevent children from smoking. Firstly, the limited period of protection provided by existing vaccines would require booster injections, perhaps every 2–3 months throughout adolescence.[48] Secondly, the vaccine can be circumvented by using larger than usual doses of nicotine. Thirdly, vaccination could also have counterproductive effects if adolescents were tempted to test the vaccine's efficacy by smoking at a higher rate. Fourthly, it would be expensive to universally vaccinate children using a vaccine that would probably have modest efficacy. This makes universal vaccination unlikely to be publicly funded.

It would be less expensive to vaccinate only young people who were at increased ''genetic risk'' of smoking tobacco, which may make predictive genetics and nicotine vaccines seem a good combination. The feasibility of this approach looks poor given (1) the poor predictive validity of genetic screening for nicotine dependence (as outlined above); (2) the probable modest preventive efficacy of a nicotine vaccine; and (3) the possibility of unintended adverse effects of vaccination, such as stigmatisation of those who screen positive and possible discrimination against those who were vaccinated by life or health insurance companies.

SUMMARY

Given the promises made for genomic medicine, we need detailed analyses of the feasibility, likely effectiveness and cost-effectiveness, and the ethical and policy issues raised in using information on genetic risks of nicotine dependence and tobacco-related disease to increase smoking cessation or reduce tobacco-related disease. The following conjectures based on the available data need to be tested in more detailed analyses as better data come to hand.

New genetic and immunological biotechnologies have the potential to increase the modest success rates of current smoking cessation programmes. On the basis of available data, new pharmacological cessation treatments and nicotine vaccines look more promising than screening smokers for polymorphisms that predict responses to existing, modestly effective pharmacological treatments for smoking cessation. Better empirical data and epidemiological and economic modelling of the comparative cost effectiveness of these approaches is needed to assist policy makers in deciding which of these approaches to support. We also need to evaluate the effects of providing genetic risk information on self-efficacy and beliefs of smokers that may affect their willingness to quit smoking and the interest of current smokers in using nicotine vaccines for smoking cessation.

The preventive use of biotechnologies—screening the population for genetic susceptibility to nicotine dependence, screening smokers for polymorphisms that predict increased susceptibility to tobacco-related diseases, and vaccinating non-smoking children against the effects of nicotine—are more speculative policy options. Given the current data, their likely efficacy and cost-effectiveness look doubtful. Population screening for multiple susceptibility genes for nicotine dependence is a poor public policy because there is no good reason for anyone to smoke tobacco. It also faces major technical challenges—namely, the polymorphisms identified to date weakly predict the risk for most people; it will be costly to screen large numbers of people to identify the small number at highest risk; there are no effective interventions for those identified as at risk; and screening may have counterproductive

What this paper adds

- Twin studies have indicated that genes contribute to nicotine dependence. These may include genes that affect nicotine metabolism and the effects of nicotine on brain neurotransmitters.
- This paper describes the potential therapeutic and preventive applications of recent research on the genetics and neurobiology of nicotine dependence.
- It also identifies research priorities in evaluating their cost effectiveness, and the social and ethical issues that their use may raise.

effects. The impracticality of population screening for genes that predict low risk of smokers developing smoking-related diseases is increased by the large number of susceptibility genes that will need to be screened for and the very small chance that many smokers will be at low risk of developing all of the major diseases caused by tobacco smoking.

Even if these new technologies prove successful, it will remain cheaper and more efficient to implement them in a tobacco policy setting in which we continue to use taxation and other policies to discourage the whole population from smoking tobacco.[78 79] A challenging task for social science research will be assessing the effects that these genetic technologies may have on public understanding of tobacco use and public support for tobacco control policies.[80]

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